Final report-Teratologic Evaluation of FDA 71-9 (Sodium Nitrite) in Mice, Rats, Hamsters & Rabbits 7/3/72 #23

#28

FOOD AND DRUG LABORATORIES, INC.

MAURICE AVENUE AT 58TH STREET, MASPETH, NEW YORK 11378

FINAL

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FINAL

July 3, 1972

Teratologic Evaluation of FDA 71-9

(Sodium Nitrite)

in

Mice, Rats, Hamsters and Rabbits

Food and Drug Research Laboratories
INCORPORATED

Waverly Division
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July 14, 1972

COPY

Mr. L. C. Appleby, Contracts Officer
Department of Health, Education and Welfare
Food and Drug Administration
Contracts Section CA-272
Contracts and Grants Branch
5600 Fishers Lane
Rockville, Maryland 20852

Subject: Teratologic Studies, Final Reports
Re: FDA Contract No. 71-260

Dear Mr. Appleby:

We are today forwarding final reports covering teratologic studies on FDA Compounds 71-9 and 71-10 as follows:

Your office	1 copy (via Mr. Carle's office)
Dr. Alan Spiher	2 copies
Dr. Joseph McLaughlin	2 copies

These final copies correspond to drafts dated May 31, 1972.

If you have any further instructions, or questions, please do not hesitate to contact us.

Cordially,

FOOD and DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

KM:d
cc: Dr. Alan Spiher
Dr. Joseph McLaughlin
Mr. D. A. Carle

M I C E

Food and Drug Research Laboratories
INCORPORATED

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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 3, 1972

Laboratory No. 0728 1
Contract No. FDA 71-260

Sample: Light yellow crystalline material

Marking: FDA 71-9 (Sodium nitrite)

Examination Requested: Teratologic evaluation of FDA 71-9 in mice.

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 56 mg/kg (body weight) of the test material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the sixth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 51 through 56

Material: FDA 71-9

Date May 31, 1972

Laboratory No. 0728 1

Table 1

Fate Summary
(Mice)

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
51	Sham	0	23	22	23	22
52	Aspirin*	150	32	24	30	21
53	FDA 71-9	0.2	22	21	22	21
54	FDA 71-9	1.1	22	20	22	20
55	FDA 71-9	5.0	26	20	26	20
56	FDA 71-9	23.0	25	21	25	21

* Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 51 through 56 Date May 31, 1972

Material: FDA 71-9 Laboratory No. 0728 1

Table 2
Reproduction Data
(Mice)

Group:	51	52	53	54	55	56
Dose (mg/kg):	Sham	Aspirin**	0.2	1.1	5.0	23.0
Pregnancies						
Total No.	22	24	21	20	20	21
Died or aborted (before Day 17)	0	3	0	0	0	0
To term (on Day 17)	22	21	21	20	20	21
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	22	21	21	20	20	21
Implant sites						
Total No. (at term)	268	254	255	243	246	267
Average/dam*	12.2	12.1	13.1	12.2	12.3	12.7
Resorptions						
Total No.*	18	13	13	15	12	15
Dams with 1 or more sites resorbed	8	8	10	10	10	11
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	36.4	38.1	47.6	50.0	50.0	52.4
Per cent complete resorptions	-	-	-	-	-	-
Live fetuses						
Total No. (at term)	249	232	240	224	233	250
Average/dam*	11.3	11.0	11.5	11.2	11.7	11.9
Dead fetuses						
Total No.*	1	5	2	4	1	2
Dams with 1 or more dead	1	3	2	4	1	2
Dams with all dead	0	0	0	0	0	0
Per cent partial dead	4.55	14.3	9.52	20.0	10.0	9.52
per cent all dead	-	-	-	-	-	-
Average fetus weight, g	0.96	0.83	1.01	0.99	1.01	0.97

* Includes only those dams examined at term.

** Positive control: 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56 — Laboratory No. 0728 1

Table 3

Material FDA 71-3 — Date May 31, 1972

Summary of Skeletal Findings
(Mice)

Findings	Group No. / Dose (mg/kg)	51 Sham	52 Aspirin**	53 0.2	54 1.1	55 5.0	56 23.0
Live Fetuses Examined (at term)		171/22	156/21	167/21	158/20	152/20	173/21
Sternebrae							
Incomplete oss.		45/14	52/12	37/14	45/13	37/13	47/12
Scrambled							
Bipartite		8/7	4/3	4/5	4/3		
Fused				1/1			
Extra		1/1		2/2		1/1	1/1
Missing		11/4	51/8	3/1	7/6	3/2	13/6
Other							
Ribs							
Incomplete oss.					4/1		1/1
Fused/split			3/1				
Wavy			1/1			1/1	
Less than 12							
More than 13		15/9	36/10	14/7	21/11	31/10	36/16
Other (Missing)			1/1				
Vertebrae							
Incomplete oss.		2/2			2/1		
Scrambled							
Fused							
Extra ctrs. oss.							
Scoliosis		2/2	1/1	2/2	1/1	3/2	1/1
Tail defects							
Other							
Skull							
Incomplete closure		4/2		1/1	6/3		
Missing							
Craniostosis							
Other : occipitals; missing			25/5				
Extremities							
Incomplete oss.		3/2	3/3		2/2		
Missing							
Extra							
Miscellaneous							
Hyoid; missing		12/10	50/3	19/6	11/7	21/8	34/11
Hyoid; reduced		23/8	27/11	18/11	24/13	21/16	13/10

* Numerator=Number of fetuses affected; Denominator=Number of litters affected.
** Positive control 150 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56 Date May 31, 1972

Material FDA 71-9 Laboratory No. 07281

Table 3-a

Summary of Soft Tissue Abnormalities

(Mice)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
54	FDA 71-9	1.1	L 8037	1	Meningocraniocoele
56	FDA 71-9	23.0	L 8111	1	Meningocraniocoele
56	FDA 71-9	23.0	L 8114	1	Meningocraniocoele

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56

Species Mice

Table 4

Average Body Weights*

Date May 31, 1972

Laboratory No. 0728 1

Group	Material	Dose Level	Day 0	6	11	15	17	**
		mg/kg	g					
51	Sham	0	30.2	31.0	36.0	44.6	50.6	(22)
52	Aspirin***	150	29.0	32.5	34.0	43.1	47.6	(21)
53	FDA 71-9	0.2	29.2	32.0	36.7	45.2	50.7	(21)
54	FDA 71-9	1.1	27.9	31.9	35.1	44.4	50.6	(20)
55	FDA 71-9	5.0	30.0	34.0	37.1	47.7	53.3	(20)
56	FDA 71-9	23.0	29.3	32.5	36.3	46.0	52.8	(21)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control:

Appendix I

Teratology Study in Mice

Virgin adult female albino CD-1 outbred mice were individually housed in disposable plastic cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 17 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 17 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 51 | Appendix II | Date May 31, 1972

Material Sham | Reproduction Data in Mice (Individual) | Laboratory No. 0728

Dose 0

Dam No.	Fate *	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
S 8151	P	11	10		1	0.96	
S 8152	P	12	12			1.35	
S 8153	P	12	12			0.87	
S 8154	NP	0				----	
S 8155	P	11	11			1.13	
S 8156	P	13	13			1.01	
S 8157	P	11	11			1.11	
S 8158	P	12	12			1.02	
S 8159	P	14	12		2	1.05	
S 8160	P	15	12	1	2	0.87	
S 8161	P	12	12			1.00	
S 8162	P	14	14			0.86	
S 8163	P	13	12		1	0.93	
S 8164	P	11	10		1	0.85	
S 8165	P	12	12			1.02	
S 8166	P	13	13			0.95	
S 8167	P	11	11			0.97	
S 8168	P	14	14			1.00	
S 8169	P	12	10		2	1.01	
S 8170	P	12	12			1.01	
S 8171	P	11	3		8	0.80	
S 8172	P	10	9		1	0.73	
S 8173	P	12	12			0.68	

* P= Pregnant; NP= Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 52 | Appendix II | Date May 31, 1972

Material Aspirin | Reproduction Data in Mice (Individual) | Laboratory No. 0728

Dose 150 mg/kg

Dam No.	Fate *	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
A 8151	P	14			14	----	Died Day 14.
A 8152	P	13	9		4	0.88	
A 8153	P	14	13		1	0.66	
A 8154	P	13			13	----	Died Day 15.
A 8155	P	14	10		4	0.77	
A 8156	P	14	14			0.71	
A 8157	P	11	11			0.83	
A 8158	P	10	10			0.65	
A 8159	-	-				----	Not assigned.
A 8160	NP	0				----	
A 8161	P	11	10		1	0.85	
A 8162	P	13	13			0.93	
A 8163	P	15	13	2		1.00	
A 8164	-	-				----	Not assigned.
A 8165	P	10	10			1.12	
A 8166	NP	0				----	
A 8167	P	12		12		----	Died Day 16
A 8168	P	13	13			0.95	
A 8169	NP	0				----	
A 8170	NP	0				----	
A 8171	P	15	12	2	1	0.62	
A 8172	NP	0				----	
A 8173	NP	0				----	
A 8174	P	13	12		1	0.63	
A 8175	NP	0				----	
A 8176	NP	0				----	
A 8177	P	14	12		2	0.48	
A 8178	P	14	10	1	3	0.77	
A 8179	P	12	12			0.90	
A 8180	P	12	12			0.86	
A 8180 I	P	13	13			0.99	
A 8180 II	P	9	9			0.61	
A 8180 III	P	12	12			1.15	
A 8180 IV	P	2	2			1.15	

* P= Pregnant; NP = Not Pregnant

R A T S

Food and Drug Research Laboratories
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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 3, 1972

Laboratory No. 0729 1
Contract No. FDA 71-260

Sample: Light yellow crystalline material

Marking: FDA 71-9 (Sodium nitrite)

Examination Requested: Teratologic evaluation of FDA 71-9 in rats

Procedure: See Appendix I

sults: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 3.0 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no discernible effect on nidation, or on maternal or fetal survival. At this dose level, the number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls. However, at a dose level of 10.0 mg/kg (body weight), there were slight indications of delayed skeletal maturation, particularly with respect to ribs and skull. Outright increase in terata were not observed nor did this dose cause any alteration in nidation or fetal survival. It was concluded that this test material is not a frank teratogen for the rat under the experimental conditions employed."

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

Comment: Attention is called to the fact that this is the sixth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 51 through 56

Material: FDA 71-9

Table 1

Fate Summary
(Rats)

Date May 31, 1972

Laboratory No. 0729 1

Group	Material	Dose mg/kg	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
51	Sham	0	22	21	22	21
52	Aspirin	250	22	22	22	22
53	FDA 71-9	0.1	23	21	23	21
54	FDA 71-9	0.5	22	21	22	21
55	FDA 71-9	3.0	23	23	23	23
56	FDA 71-9	10.0	23	21	23	21

* Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 51 through 56 Date May 31, 1972

Material: FDA 71-9 Laboratory No. 0729 1

Table 2
Reproduction Data
(Rats)

Group:	51	52	53	54	55	56
Dose (mg/kg):	Sham	Aspirin**	0.1	0.5	3.0	10.0
Pregnancies						
Total No.	21	22	21	21	23	21
Died or aborted (before Day 20)	0	0	0	0	0	0
To term (on Day 20)	21	22	21	21	23	21
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	21	10	21	21	23	21
Implant sites						
Total No. (at term)	229	239	234	252	253	238
Average/dam*	10.9	10.9	11.1	12.0	11.0	11.3
Resorptions						
Total No.*	15	144	0	13	9	4
Dams with 1 or more sites resorbed	6	18	-	5	6	4
Dams with all sites resorbed	0	12	-	0	0	0
Per cent partial resorptions	28.6	81.8	-	23.8	26.1	19.0
Per cent complete resorptions	-	54.5	-	-	-	-
Live fetuses						
Total No. (at term)	214	92	234	239	244	234
Average/dam*	10.2	4.18	11.1	11.4	10.6	11.1
Dead fetuses						
Total No.*	0	3	0	0	0	0
Dams with 1 or more dead	-	2	-	-	-	-
Dams with all dead	-	0	-	-	-	-
Per cent partial dead	-	9.09	-	-	-	-
per cent all dead	-	-	-	-	-	-
Average fetus weight, g	3.75	2.19	3.73	3.87	3.92	3.89

* Includes only those dams examined at term.
** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56 | Laboratory No. 07291

Table 3

Material FDA 71-9 | Date May 31, 1972

Summary of Skeletal Findings
(Rats)

Findings	Group No. / Dose (mg/kg)	51 Sham	52 ** Aspirin	53 0.1	54 0.5	55 3.0	56 10.0
Live Fetuses Examined (at term)		215/21	52/9[a]	234/21	239/21	244/23	234/21
Sternebrae							
Incomplete oss.		11/8	38/9	16/12	17/10	12/7	28/15
Scrambled							
Bipartite							
Fused							
Extra							
Missing				1/1		1/1	1/1
Other							
Ribs							
Incomplete oss.			5/3				
Fused/split			11/5				
Wavy		4/4	26/8	3/3	1/1	2/2	13/7
Less than 12			3/3				
More than 13			12/7				
Other							
Vertebrae							
Incomplete oss.		2/2	40/7	4/4	1/1	2/2	6/6
Scrambled							
Fused			1/1				
Extra ctrs. oss.							
Scoliosis			3/3				
Tail defects							
Other							
Skull							
Incomplete closure		8/5	44/9	3/3	2/2	4/3	19/7
Missing							
Craniostosis							
Other							
Extremities							
Incomplete oss.		1/1	1/1				
Missing							
Extra							
Miscellaneous							
Hyoid; missing		4/2	44/9	3/1	7/6	6/4	12/7
Hyoid; reduced		3/2	1/1	6/5	2/1	2/2	6/5

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
** Positive control at 250 mg/kg
a.) One litter lost

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56 Date May 31, 1972

Material FDA 71-9 Laboratory No. 07291

Table 3-a

Summary of Soft Tissue Abnormalities

(Rats)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
51	Sham	0	S 9153	1	Cervical subcutaneous hematoma
			S 9154	1	Cervical subcutaneous hematoma
			S 9155	2	Cervical subcutaneous hematoma
			S 9156	1	Cervical subcutaneous hematoma
52	Aspirin	250	A 9152	2 1	Enterohepatocoele Acrania, spina bifida
			A 9161	3	Acrania, spina bifida
			A 9162	2	Acrania, spina bifida
			A 9168	1	Acrania, spina bifida, craniocoele
			A 9170	3 1	Acrania Spina bifida
53	FDA 71-9	0.1	L 9014	1	Acrania
55	FDA 71-9	3.0	L 9068	1	Sacral subcutaneous hematoma
			L 9071	1	Cervical subcutaneous hematoma
			L 9099	1	Cervical subcutaneous hematoma
			L 9104	1	Cervical subcutaneous hematoma

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56

Species Rats

Table 4

Average Body Weights*

Date May 31, 1972

Laboratory No. 0729 1

Group	Material	Dose Level	Day 0	6	11	15	20	**
		mg/kg	g					
51	Sham	0	203	219	239	266	330	(21)
52	Aspirin***	250	205	224	242	261	293	(22)
53	FDA 71-9	0.1	205	222	249	273	342	(21)
54	FDA 71-9	0.5	209	230	254	279	348	(21)
55	FDA 71-9	3.0	209	227	252	277	342	(23)
56	FDA 71-9	10.0	206	224	246	273	339	(21)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control:

Appendix I

Teratology Study in Rats

Virgin adult female albino rats (Wistar derived stock) were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. They were mated with young adult males, and observation of the vaginal sperm plug was considered Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 15 of gestation, the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 11, 15, and 20 of gestation. All animals were observed daily for appearance and behavior with particular attention to food consumption and weight, in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 20 all dams were subjected to Caesarean section under surgical anesthesia, and the numbers of implantation sites, resorption sites, and live and dead fetuses were recorded. The body weights of the live pups were also recorded. The urogenital tract of each dam was examined in detail for anatomical normality.

All fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses of each litter underwent detailed visceral examinations employing 10X magnification. The remaining two-thirds were cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 51 | Appendix II | Date May 31, 1972

Material Sham | Reproduction Data in Rats (Individual) | Laboratory No. 0729

Dose 0

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
S 9151	P	4	4			5.6	
S 9152	P	11	11			3.6	
S 9153	P	14	14			4.1	
S 9154	P	11	11			3.5	
S 9155	P	12	12			3.5	
S 9156	P	11	11			3.8	
S 9157	P	12	11		1	3.7	
S 9158	P	11	11			3.5	
S 9159	P	10	10			3.4	
S 9160	P	12	11		1	3.2	
S 9161	P	10	10			5.4	
S 9162	P	11	11			3.3	
S 9163	P	11	10		1	3.6	
S 9164	P	14	14			3.3	
S 9165	P	12	11		1	3.5	
S 9166	P	9	9			3.7	
S 9167	P	9	3		6	3.8	
S 9168	NP	0				---	
S 9169	P	12	12			3.6	
S 9170	P	11	11			3.8	
S 9171	P	14	9		5	3.4	
S 9172	P	8	8			3.6	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 52 | Appendix II | Date May 31, 1972

Material Aspirin | Reproduction Data in Rats (Individual) | Laboratory No. 0729

Dose 250 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
A 9151	P	6			6	---	
A 9152	P	11	9	2		2.1	
A 9153	P	9			9	---	
A 9154	P	12			12	---	
A 9155	P	15	10		5	2.1	
A 9156	P	10			10	---	
A 9157	P	10			10	---	
A 9158	P	9	4		5	1.9	
A 9159	P	12			12	---	
A 9160	P	10			10	---	
A 9161	P	11	9		2	2.4	
A 9162	P	12	10	1	1	2.1	
A 9163	P	7			7	---	
A 9164	P	9			9	---	
A 9165	P	11	2		9	1.7	
A 9166	P	13			13	---	
A 9167	P	15	15			2.7	
A 9168	P	13	10		3	2.0	
A 9169	P	10			10	---	
A 9170	P	12	12			2.1	
A 9171	P	11			11	---	
A 9172	P	11	11			2.8	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 53 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Rats (Individual) | Laboratory No. 0729 1

Dose 0.1 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
L 9001	P	10	10			3.9	
L 9002	P	13	13			3.7	
L 9003	P	10	10			3.7	
L 9004	P	11	11			3.7	
L 9005	P	8	8			4.2	
L 9006	P	12	12			3.6	
L 9007	P	9	9			3.8	
L 9008	P	11	11			3.9	
L 9009	P	11	11			3.8	
L 9010	P	12	12			3.8	
L 9011	P	11	11			3.7	
L 9012	P	13	13			3.7	
L 9013	P	13	13			3.7	
L 9014	P	12	12			3.4	
L 9015	NP					---	
L 9016	P	13	13			3.7	
L 9017	P	12	12			3.9	
L 9018	P	10	10			3.7	
L 9019	P	12	12			3.7	
L 9020	P	12	12			3.3	
L 9021	P	8	8			3.9	
L 9022	NP					---	
L 9023	P	11	11			3.6	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 54 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Rats (Individual) | Laboratory No. 0729 1

Dose 0.5 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
L 9031	P	14	14			4.1	
L 9032	P	10	8		2	3.8	
L 9033	P	14	14			3.9	
L 9034	P	12	10		2	3.7	
L 9035	P	10	10			4.2	
L 9036	P	10	5		5	4.2	
L 9037	P	12	12			3.7	
L 9038	P	14	13		1	4.1	
L 9039	P	13	13			4.0	
L 9040	P	11	11			3.7	
L 9041	P	14	14			3.8	
L 9042	P	15	15			3.8	
L 9043	P	11	11			3.7	
L 9044	P	15	15			3.5	
L 9045	P	10	10			3.4	
L 9046	P	11	11			3.8	
L 9047	NP					---	
L 9048	P	16	16			4.2	
L 9049	P	10	10			3.9	
L 9050	P	7	4		3	4.0	
L 9051	P	12	12			3.7	
L 9052	P	11	11			4.0	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 55 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Rats (Individual) | Laboratory No. 0729 1

Dose 3.0 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
L 9061	P	11	11			5.1	
L 9062	P	10	10			3.7	
L 9063	P	11	11			4.0	
L 9064	P	11	11			3.5	
L 9065	P	11	10		1	4.1	
L 9066	P	9	8		1	4.1	
L 9067	P	13	13			4.0	
L 9068	P	9	8		1	4.0	
L 9069	P	11	11			3.4	
L 9070	P	14	14			4.0	
L 9071	P	13	13			3.8	
L 9072	P	12	11		1	4.0	
L 9073	P	11	11			3.7	
L 9074	P	10	10			3.8	
L 9075	P	12	12			4.2	
L 9076	P	10	6		4	3.5	
L 9077	P	13	13			3.7	
L 9078	P	15	15			3.7	
L 9079	P	4	4			4.2	
L 9080	P	14	14			3.6	
L 9081	P	11	11			4.2	
L 9082	P	9	8		1	3.8	
L 9083	P	9	9			4.0	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 56 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Rats (Individual) | Laboratory No. 0729 1

Dose 10.0 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
L 9091	P	13	13			3.7	
L 9092	P	10	10			4.0	
L 9093	NP					---	
L 9094	P	8	8			3.6	
L 9095	P	11	11			3.9	
L 9096	P	12	12			3.6	
L 9097	P	11	10		1	4.0	
L 9098	NP					---	
L 9099	P	11	10		1	3.9	
L 9100	P	16	16			3.7	
L 9101	P	12	12			3.7	
L 9102	P	5	4		1	5.2	
L 9103	P	9	9			4.7	
L 9104	P	13	13			3.6	
L 9105	P	12	12			3.8	
L 9106	P	9	8		1	3.7	
L 9107	P	12	12			3.8	
L 9108	P	13	13			4.0	
L 9109	P	13	13			3.8	
L 9110	P	12	12			3.9	
L 9111	P	15	15			3.7	
L 9112	P	9	9			3.9	
L 9113	P	12	12			3.5	

* P = Pregnant; NP = Not Pregnant

HAMSTERS

Food and Drug Research Laboratories
INCORPORATED

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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 3, 1972

Laboratory No. 0730 1
Contract No. FDA 71-260

Sample: Light yellow crystalline material

Marking: FDA 71-9 (Sodium nitrite)

Examination Requested: Teratologic evaluation of FDA 71-9 in hamsters

Procedure: See Appendix I

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 23 mg/kg (body weight) of the test material to pregnant hamsters for 5 consecutive days had no effect on nidation, or on maternal or fetal survival. The number of abnormalities occurring in soft tissues of fetuses from the test groups did not differ from the number seen in the sham-treated controls. However, the administration of this test material appeared to be associated with delayed skeletal maturation in this species which was not clearly dose-related. Whether or not the substance is teratogenic in the hamster can only be determined on the basis of further studies."

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D.
Vice President

Comment: Attention is called to the fact that this is the sixth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 51 through 56

Material: FDA 71-9

Table 1

Fate Summary
(Hamsters)

Date May 31, 1972

Laboratory No. 0730-1

Group	Material	Dose	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
51	Sham	0	24	21	24	21
52	Aspirin*	250	23	22	23	22
53	FDA 71-9	0.2	26	22	25	21
54	FDA 71-9	1.1	23	23	23	23
55	FDA 71-9	5.0	24	21	24	21
56	FDA 71-9	23	23	23	23	23

* Positive Control

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 51 through 56 Date May 31, 1972

Material: FDA 71-9 Laboratory No. 0730 1

Table 2
Reproduction Data
(Hamsters)

Group:	51	52	53	54	55	56
Dose (mg/kg):	Sham	Aspirin**	0.2	1.1	5.0	23
Pregnancies						
Total No.	21	22	22	23	21	23
Died or aborted (before Day 14)	0	0	1	0	0	0
To term (on Day 14)	21	22	21	23	21	23
Corpora lutea						
Total No.						
Average/dam mated						
Live litters						
Total No.*	21	22	21	23	21	23
Implant sites						
Total No. (at term)	255	271	260	293	256	291
Average/dam*	12.1	12.3	12.4	12.7	12.2	12.6
Resorptions						
Total No.*	11	9	15	14	15	8
Dams with 1 or more sites resorbed	8	7	8	9	6	5
Dams with all sites resorbed	0	0	0	0	0	0
Per cent partial resorptions	38.1	31.8	38.1	39.1	28.6	21.7
Per cent complete resorptions	-	-	-	-	-	-
Live fetuses						
Total No. (at term)	243	262	245	278	240	282
Average/dam*	11.6	11.9	11.7	12.1	11.4	12.2
Dead fetuses						
Total No.*	1	0	0	1	1	1
Dams with 1 or more dead	1	-	-	1	1	1
Dams with all dead	0	-	-	0	0	0
Per cent partial dead	4.76	-	-	4.35	4.76	4.35
per cent all dead	-	-	-	-	-	-
Average fetus weight, g	1.87	1.74	1.78	1.80	1.82	1.81

* Includes only those dams examined at term.

** Positive control: 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56 | Table 3 | Laboratory No. 0730 1

Material FDA 71-9 | Date May 31, 1972

Summary of Skeletal Findings
(Hamsters)

Findings	Group No. / Dose (mg/kg)	51 Sham	52 Aspirin**	53 0.2	54 1.1	55 5.0	56 23.0
Live Fetuses Examined (at term)		166/21	183/22	168/21	195/23	168/21	196/23
Sternebrae							
Incomplete oss.		106/21	124/22	119/21	134/23	94/21	132/23
Scrambled							
Bipartite		56/17	91/21	69/20	63/16	67/20	84/22
Fused							
Extra		8/6	1/1	1/1	2/2	3/3	3/3
Missing		27/14	84/16	56/17	47/15	44/18	79/18
Other							
Ribs							
Incomplete oss.							1/1
Fused/split			1/1				1/1
Wavy							1/1
Less than 12							
More than 13		17/9	33/15	12/8	17/10	24/15	24/10
Other							
Vertebrae							
Incomplete oss.			3/2				
Scrambled			4/2				
Fused							
Extra ctrs. oss.		1/1	2/1				
Scoliosis		1/1	7/4	9/7	2/2	3/3	5/3
Tail defects							
Other							
Skull							
Incomplete closure		1/1	5/2	4/3	5/4	6/4	11/7
Missing							
Craniostosis							
Other: exencephaly							1/1
Extremities							
Incomplete oss.		3/1	26/10				
Missing							
Extra							
Miscellaneous							
Hyoid; reduced		1/1	7/4	1/1	5/3		6/4
Hyoid; missing			11/4		1/1	2/1	

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
** Positive control; 250 mg/kg

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56 Date May 31, 1972

Material FDA 71-9 Laboratory No. 07301

Table 3-a

Summary of Soft Tissue Abnormalities

(Hamsters)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
54	FDA 71-9	1.1	L 0040	1	Generalized edema

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56

Species Hamster

Table 4

Average Body Weights *

Date May 31, 1972

Laboratory No. 0730 L

Group	Material	Dose Level	Day 0	6	8	10	14**
		mg/kg	g				
51	Sham	0	97.3	101.4	105.8	115.2	138.5 (21)
52	Aspirin***	250	97.7	102.9	104.3	114.7	137.3 (22)
53	FDA 71-9	0.2	92.3	99.4	103.9	113.4	137.1 (21)
54	FDA 71-9	1.1	96.1	101.6	105.3	116.0	139.2 (23)
55	FDA 71-9	5.0	96.2	101.6	105.4	114.9	138.8 (21)
56	FDA 71-9	23	95.6	102.2	105.3	115.8	140.1 (23)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control:

Appendix I

Teratology Study in Hamsters

Virgin adult female golden hamsters from an outbred strain were individually housed in mesh bottom cages in temperature and humidity controlled quarters with free access to food and fresh tap water at all times. They were mated (1 to 1) with mature males and the appearance of motile sperm in the vaginal smear was considered as Day 0 of gestation. Beginning on Day 6 and continuing daily through Day 10 of gestation, the indicated dose levels of the test material were administered by oral intubation; the controls were sham-treated.

Body weights were recorded on Days 0, 8, 10, and 14 of the gestation period. All animals were observed daily for appearance and behavior with particular attention to food consumption in order to better recognize any abnormalities resulting from anorexic effects in the pregnant animal.

On Day 14, all animals were subjected to Caesarian section under deep anesthesia and the numbers of implantation sites, resorption sites, live and dead fetuses were recorded. All live pups were weighed and the genital tract of each dam was examined for any anatomical abnormalities.

All fetuses were examined grossly for the presence of external congenital defects and one-third of each litter underwent detailed visceral examination under 10X magnification. The remaining two-thirds of the pups were cleared in potassium hydroxide, stained with alizarin red dye, and examined for the presence of sketal abnormalities.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 51 | Appendix II | Date May 31, 1972

Material Sham | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730

Dose 0

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
S 0151	P	9	9			1.59	
S 0152	P	12	12			1.93	
S 0153	P	14	14			1.67	
S 0154	P	14	12	1	1	1.81	
S 0155	P	12	12			2.00	
S 0156	P	11	10		1	1.89	
S 0157	P	11	11			1.90	
S 0158	P	13	13			1.73	
S 0159	P	10	10			2.23	
S 0160	NP					----	
S 0161	P	13	12		1	1.48	
S 0162	NP					----	
S 0163	P	14	13		1	1.93	
S 0164	P	14	11		3	2.04	
S 0165	P	10	10			1.73	
S 0166	P	15	15			1.83	
S 0167	P	11	10		1	1.89	
S 0168	P	11	9		2	1.87	
S 0169	NP					----	
S 0170	P	11	11			1.90	
S 0171	P	11	11			2.04	
S 0172	P	13	12		1	1.87	
S 0173	P	12	12			1.80	
S 0174	P	14	14			2.07	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 52 | Appendix II | Date May 31, 1972

Material Aspirin | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730

Dose 250 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
A 0151	P	15	15			1.71	
A 0152	P	10	10			1.79	
A 0153	P	14	13		1	2.03	
A 0154	P	15	14		1	1.90	
A 0155	P	15	15			1.79	
A 0156	NP					----	
A 0157	P	14	14			1.71	
A 0158	P	11	10		1	1.85	
A 0159	P	12	12			1.69	
A 0160	P	12	12			1.71	
A 0161	P	10	10			0.90	
A 0162	P	13	13			1.73	
A 0163	P	14	12		2	1.87	
A 0164	P	12	12			1.55	
A 0165	P	12	10		2	1.85	
A 0166	P	11	11			1.82	
A 0167	P	15	14		1	1.54	
A 0168	P	11	11			1.80	
A 0169	P	11	11			1.92	
A 0170	P	11	10		1	1.80	
A 0171	P	10	10			1.67	
A 0172	P	10	10			1.90	
A 0173	P	13	13			1.81	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 53 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730 1

Dose 0.2 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
L 0001	P	10	10			1.76	
L 0002	P	12	12			1.78	
L 0003	P	11	11			2.03	
L 0004	NP					----	
L 0005	P	10	10			2.08	
L 0006	P	11	11			1.65	
L 0007	P	13	9		4	1.86	
L 0008	P	12	12			1.71	
L 0009	NP					----	
L 0010	P	17	14		3	1.71	
L 0011	P	12	12			1.70	
L 0012	NP					----	
L 0013	P	12	12			1.68	
L 0014	NP					----	
L 0015	-					----	Not assigned.
L 0016	P	10	10			----	Died Day 6.
L 0017	P	11	10		1	1.74	
L 0018	P	13	13			1.69	
L 0019	P	12	12			1.86	
L 0020	P	12	12			1.74	
L 0021	P	13	11		2	1.57	
L 0022	P	13	12		1	1.54	
L 0023	P	12	12			1.91	
L 0024	P	12	12			1.87	
L 0025	P	13	12		1	1.82	
L 0026	P	16	14		2	1.88	
L 0027	P	13	12		1	1.90	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 54 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730 1

Dose 1.1 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
L 0031	P	10	10			2.06	
L 0032	P	9	9			1.83	
L 0033	P	15	13		2	1.70	
L 0034	P	14	13		1	2.02	
L 0035	P	16	16			1.85	
L 0036	P	12	12			1.83	
L 0037	P	9	8		1	1.85	
L 0038	P	13	13			1.84	
L 0039	P	13	13			1.87	
L 0040	P	12	10	1	1	1.74	
L 0041	P	14	13		1	1.63	
L 0042	P	11	11			1.86	
L 0043	P	11	11			1.76	
L 0044	P	15	14		1	1.65	
L 0045	P	17	17			1.42	
L 0046	P	13	13			1.94	
L 0047	P	13	10		3	1.96	
L 0048	P	10	10			1.76	
L 0049	P	12	10		2	1.80	
L 0050	P	12	12			1.79	
L 0051	P	11	11			1.82	
L 0052	P	17	17			1.70	
L 0053	P	14	12		2	1.78	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 55 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Hamsters (Individual) | Laboratory No. 0730 1

Dose 5.0 mg/kg

Dam No.	Fate*	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
			Alive	Dead			
L 0061	P	12	12			2.04	
L 0062	P	14	13		1	2.10	
L 0063	P	8	8			1.95	
L 0064	P	14	11	1	2	1.67	
L 0065	P	10	8		2	1.92	
L 0066	NP					----	
L 0067	P	13	13			1.76	
L 0068	P	13	6		7	1.81	
L 0069	P	13	13			1.76	
L 0070	P	11	11			1.62	
L 0071	P	14	14			1.64	
L 0072	P	11	11			1.59	
L 0073	P	14	12		2	1.77	
L 0074	P	13	13			1.70	
L 0075	P	13	13			2.00	
L 0076	P	11	11			1.85	
L 0077	P	12	12			1.97	
L 0078	NP					----	
L 0079	P	11	10		1	1.83	
L 0080	P	12	12			1.91	
L 0081	P	13	13			1.93	
L 0082	NP					----	
L 0083	P	11	11			1.85	
L 0084	P	13	13			1.64	

* P = Pregnant; NP = Not Pregnant

RABBITS

Food and Drug Research Laboratories
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FINAL REPORT

Submitted to: DHEW/Public Health Service
Food and Drug Administration CA-272
5600 Fishers Lane-Room 5C-13
Rockville, Maryland 20852

Date July 3, 1972

Laboratory No. 0731 1
Contract No. FDA 71-260

Sample: Light yellow crystalline material

Marking: FDA 71-9 (Sodium nitrite)

Examination Requested: Teratologic evaluation of FDA 71-9 in rabbits

Procedure: (See Appendix I)

Results: See Tables 1 through 4 and Appendix II

Conclusion: Subject to reexamination in the light of later findings, the following is concluded:

"The administration of up to 23 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls."

Comment: Attention is called to the fact that this is the sixth of a series of reports which will be issued in accordance with the terms of the contract cited above. Eventually, a total of at least 36 compounds will have been tested in 18 pairs; each pair being run concurrently against one sham-treated control and one positive control group. Because of the inherent variability of biological data of the type dealt with here, the accumulation and pooling of sequential sets of control values will greatly enhance the statistical value of the findings and the ultimate reliability of the test results.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Kenneth Morgareidge

Kenneth Morgareidge, Ph.D
Vice President

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups: 51 through 56

Material: FDA 71-9

Table 1

Fate Summary
(Rabbits)

Date May 31, 1972

Laboratory No. 0731 1

Group	Material	Dose	Total		At Term	
			Mated	Pregnant	Surviving (Total)	Number Pregnant
51	Sham	0	15	10	6	4
52	6-AN*	1.5	15	12	15	12
53	FDA 71-9	0.2	15	10	9	5
54	FDA 71-9	1.1	15	11	11	8
55	FDA 71-9	5.0	15	12	7	5
56	FDA 71-9	23.0	15	11	10	6

* Positive Control: 6 amino nicotinamide dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group: 51 through 56 Date May 31, 1972

Material: FDA 71-9 Laboratory No. 0731 1

Table 2
Reproduction Data
(Rabbits)

Group:	51	52	53	54	55	56
Dose (mg/kg):	Sham	6-AN**	0.2	1.1	5.0	23.0
Pregnancies						
Total No.	10	12	10	11	12	11
Died or aborted (before Day 29)	9	0	7	4	8	5
To term (on Day 29)	4	12	5	8	5	6
Corpora lutea						
Total No.	186	146	138	160	175	174
Average/dam mated	12.4	9.73	9.20	10.7	11.7	11.6
Live litters						
Total No.*	4	8	2	7	3	4
Implant sites						
Total No. (at term)	29	58	21	47	25	30
Average/dam*	7.25	4.83	4.20	5.88	5.00	5.00
Resorptions						
Total No.*	0	15	11	23	6	8
Dams with 1 or more sites resorbed	--	8	3	6	3	4
Dams with all sites resorbed	--	4	3	1	2	2
Per cent partial resorptions	--	66.7	60.0	75.0	60.0	66.7
Per cent complete resorptions	--	33.3	60.0	12.5	40.0	33.3
Live fetuses						
Total No. (at term)	29	38	10	23	19	22
Average/dam*	7.25	3.17	2.00	2.88	3.80	3.67
Dead fetuses						
Total No.*	0	5	0	1	0	0
Dams with 1 or more dead	--	1	--	1	--	--
Dams with all dead	--	1	--	0	--	--
Per cent partial dead	--	8.33	--	12.5	--	--
per cent all dead	--	8.33	--	--	--	--
Average fetus weight, g	37.5	30.8	37.4	43.9	35.8	37.6

* Includes only those dams examined at term.

** Positive control: 2.5 mg/kg 6-amino nicotinamide dosed on Day 9.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56 | Laboratory No. 0731 1

Table 3

Material FDA 71-9 | Date May 31, 1972

Summary of Skeletal Findings
(Rabbits)

Findings	Group No.	51	52	53	54	55	56
	Dose (mg/kg)	Sham	6-AN**	0.2	1.1	5.0	23.0
Live Fetuses Examined (at term)		29/4	38/8	10/2	23/7	19/3	22/4
Sternebrae							
Incomplete oss.			15/6			6/3	3/3
Scrambled			1/1				
Bipartite			4/2		1/1	1/1	1/1
Fused		1/1	6/4			1/1	1/1
Extra			2/2			1/1	
Missing							
Other							
Ribs							
Incomplete oss.							
Fused/split			29/8				
Wavy							
Less than 12							
More than 13						1/1	
Other							
Vertebrae							
Incomplete oss.							
Scrambled			9/3				
Fused							
Extra ctrs. oss.							
Scoliosis							
Tail defects			30/7				
Other							
Skull							
Incomplete closure							
Missing							
Craniostosis						2/1	
Other							
Extremities							
Incomplete oss.			2/1				
Missing							
Extra; Feet, elongated			1/1				
Miscellaneous							

* Numerator=Number of fetuses affected; Denominator=Number of litters affected
** Positive control: 2.5 mg/kg dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56 Date May 31, 1972

Material FDA 71-9 Laboratory No. 0731 1

Table 3-a

Summary of Soft Tissue Abnormalities

(Rabbits)

Group	Material	Dose level mg/kg	Dam	Number of Pups	Description
52	6-AN*	1.5	Z 1081	6	Anopia
				2	Club feet
			Z 1082	6	Anopia
				6	Club feet
				6	Cleft palate, hair lip
			Z 1084	5	Anopia
				2	Club feet
			Z 1085	2	Cleft palate, hair lip
				2	Anopia
				2	Craniostenosis
				2	Club feet
			Z 1086	4	Anopia
				4	Club feet
			Z 1088	4	Anopia
				4	Club feet
			Z 1089	6	Anopia
				6	Club feet
56	FDA 71-9	23.0	L 1058	1	Macrophthalmia

* 6 amino nicotinamide (positive control) dosed on Day 9

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Groups 51 through 56

Species Rabbits

Table 4

Average Body Weights*

Date May 31, 1972

Laboratory No. 0731 1

Group	Material	Dose Level	Day 0	6	12	18	29**
		mg/kg	kg				
51	Sham	0	2.48	2.49	2.54	2.55	2.36 (4)
52	6-AN***	1.5	2.28	2.34	2.33	2.36	2.49 (12)[a]
53	FDA 71-9	0.2	2.14	2.19	2.20	2.18	2.07 (5)
54	FDA 71-9	1.1	2.45	2.46	2.51	2.56	2.77 (8)[a]
55	FDA 71-9	5.0	2.27	2.31	2.33	2.32	2.37 (5)
56	FDA 71-9	23.0	2.73	2.72	2.70	2.59	2.74 (6)

* Of pregnant dams
** Number of surviving dams in parentheses (c.f. Table 1)
*** Positive control: 6-amino nicotinamide dosed on Day 9
a) Terminal weight of Z 1090 and L 1029 respectively not included in average (c.f. Appendix II)

Appendix I

Teratology Study in Rabbits

Virgin, adult, Dutch-belted female rabbits were individually housed in mesh bottom cages in temperature and humidity-controlled quarters with free access to food and fresh tap water. On Day 0, each doe was given an injection of 0.4 ml of human chorionic gonadotropin (400 IU) via the marginal ear vein. Three hours later, each doe was inseminated artificially with 0.3 ml of diluted semen from a proven donor buck using approximately 20×10^6 motile sperm according to the procedure described by Vogin et al (Pharmacologist 11, 282 (1969)). Beginning on Day 6 and continuing daily through Day 18 the females were dosed with the indicated dosages by oral intubation; the controls were sham treated.

Body weights were recorded on Days 0, 6, 12, 18, and 29 of gestation. All animals were observed daily for appearance and behavior, with particular attention to food consumption and body weight in order to rule out any abnormalities which may have occurred as a result of anorexic effects in the pregnant female animal.

On Day 29 all does were subjected to Caesarean section under surgical anesthesia, and the numbers of corpora lutea, implantation sites, resorption sites and live and dead fetuses were recorded. Body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. In addition all fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of

each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities (by dissection). All fetuses were then cleared in potassium hydroxide (KOH), stained with alizarin red S dye and examined for skeletal defects.

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 51 | Appendix II | Date May 31, 1972

Material Sham | Reproduction Data in Rabbits (Individual) | Laboratory No. 0731

Dose 0

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
S 1076	NP	1	0				--	
S 1077	NP	13	0				--	Died Day 20
S 1078	P	12	2	2			50.2	
S 1079	P	17	5	5			--	Died Day 18
S 1080	P	16	7	7			32.2	
S 1081	P	16	4	4			--	Died Day 24
S 1082	NP	4	0					
S 1083	P	25	11	11			27.7	
S 1084	P	4	1	1			--	Died Day 23
S 1085	P	16	9	9			40.0	
S 1086	NP	10	0					Died Day 12
S 1087	NP	5	0					Died Day 10
S 1088	P	8	2	2				Died Day 11
S 1089	P	18	7	7				Died Day 11
S 1090	P	21	12	12				Died Day 15

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 52 | Appendix II | Date May 31, 1972

Material 6-AN | Reproduction Data in Rabbits (Individual) | Laboratory No. 0731

Dose 1.5 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
Z 1076	P	6	2			2	--	
Z 1077	NP	4	0				--	
Z 1078	P	8	5	4		1	30.1	
Z 1079	NP	5	0				--	
Z 1080	P	9	1			1	--	
Z 1081	P	13	7	7			33.2	
Z 1082	P	12	6	6			29.2	
Z 1083	P	4	1			1	--	
Z 1084	P	14	10	5	5		36.9	
Z 1085	P	10	5	2		3	27.5	
Z 1086	P	12	6	4		2	26.1	
Z 1087	NP	3	0				--	
Z 1088	P	20	7	4		3	35.7	
Z 1089	P	17	6	6			27.4	
Z 1090	P	9	2			2	--	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 53 — Appendix II — Date May 31, 1972

Material FDA 71-9 — Reproduction Data in Rabbits (Individual) — Laboratory No. 0731 1

Dose 0.2 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
L 1001	NP	9	0				--	
L 1002	P	12	5	5			--	Died Day 14
L 1003	P	5	1	0		1	--	
L 1004	P	7	4	4			--	Died Day 22
L 1005	NP	9	0				--	
L 1006	P	13	5	5			39.9	
L 1007	P	9	6	0		6	--	
L 1008	P	12	1			1	--	Aborted Day 23
L 1009	NP	4	0				--	Died Day 26
L 1010	P	13	7	7			--	Died Day 13
L 1011	P	14	4			4	--	
L 1012	P	10	3	--			--	Died Day 7 (Accident)
L 1013	NP	6	0				--	Died Day 4
L 1014	NP	5	0				--	
L 1015	P	10	5	5			34.8	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 54 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Rabbits (Individual) | Laboratory No. 0731 1

Dose 1.1 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
L 1016	NP	4	0				--	
L 1017	P	6	1	1			--	Died Day 11
L 1018	P	22	11	6		5	43.1	
L 1019	P	9	5	3		2	46.2	
L 1020	P	8	3	3			41.5	
L 1021	NP	7	0				--	
L 1022	NP	9	0				--	Died Day 17
L 1023	P	13	8	7		1	39.4	
L 1024	P	14	8	8			--	Died Day 22
L 1025	P	13	7	1		6	40.3	
L 1026	NP	5	0				--	
L 1027	P	9	4	4			--	Died Day 8
L 1028	P	15	2	1	1		52.7	
L 1029	P	13	4			4	--	
L 1030	P	13	7	2		5	--	

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 55 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Rabbits (Individual) | Laboratory No. 0731 1

Dose 5.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
L 1031	P	6	1			1	--	
L 1032	P	7	4	0		4	--	
L 1033	NP	8	0				--	
L 1034	P	8	2					Died Day 18
L 1035	P	14	7	7			31.9	
L 1036	P	8	2	2			--	Died Day 24
L 1037	P	11	4	4				Aborted Day 15
L 1038	P	15	6	6				Died Day 18
L 1039	P	16	8	8			35.6	
L 1040	NP	11	0				--	Died Day 16
L 1041	P	10	6	6			--	Died Day 9
L 1042	P	13	8	8			--	Died Day 9
L 1043	NP	9	0					
L 1044	P	14	5	4		1	39.8	
L 1045	P	25	12	12			--	Died Day 8

* P = Pregnant; NP = Not Pregnant

FOOD AND DRUG RESEARCH LABORATORIES, INC.

Group 56 | Appendix II | Date May 31, 1972

Material FDA 71-9 | Reproduction Data in Rabbits (Individual) | Laboratory No. 0731 1

Dose 23.0 mg/kg

Dam No.	Fate*	Corpora Lutea	Implant Sites	Fetuses		Resorption Sites	Average Fetus Weight (g)	Remarks
				Alive	Dead			
L 1046	P	7	3			3	--	
L 1047	P	21	10	10			33.2	
L 1048	NP	8	0				--	
L 1049	P	24	5	2		3	31.5	
L 1050	P	21	5	4		1	50.4	
L 1051	NP	5	0				--	
L 1052	P	8	4	4			--	Died Day 12
L 1053	P	9	4	4			--	Died Day 13
L 1054	P	16	8	8			--	Died Day 11
L 1055	P	16	5	5			--	Died Day 11
L 1056	P	8	4	4			--	Died Day 9
L 1057	NP	7	0				--	
L 1058	P	12	6	6			35.1	
L 1059	P	7	1			1	--	
L 1060	NP	5	0				--	

* P = Pregnant; NP = Not Pregnant